Remarks

The Amendments to the Claims

Claim 60 has been amended to delete the recitation that "at least 50% of the" cells in the hypermutable mouse comprise a dominant negative allele of a PMS2 mismatch repair (MMR) gene. The amendment is supported by the specification which discloses a method of producing transgenic animals by "introducing the polynucleotide (transgene) into embryonic cells by infection or transfection and reintroducing the embryonic cells into the developing embryo." Page 9, lines 29-31. Such a method produces a transgenic animal having merely "cells" comprising the transgene. See page 9, line 31 to page 10, line 2 which discloses, "With this method, however, if the polynucleotide is not incorporated into germline cells, the gene will not be passed to the progeny." Thus, the specification discloses production of a transgenic animal in which some or all of its cells comprise a transgene. The amendment is supported by the specification and does not add new matter. The amendment also requires no search or further consideration because the Patent Office has already searched and considered transgenic mice comprising a dominant negative allele of a *PMS2* MMR gene. Further, the amendment to claim 60 also does not narrow the scope of claim.

Claims 61 and 71 have been amended to recite a step of "implanting the fertilized egg into a pseudopregnant female." The amendment is supported by the specification which discloses that, "According to one process of producing a transgenic animal, the polynucleotide is injected into a fertilized egg of the animal and the injected egg is placed into a pseudopregnant female." Page 9, lines 22-24. The amendment is also supported by dependent claim 70, now canceled. Thus this amendment adds no new matter. The amendment to claims 61 and 71 also

requires no further search or examination, as the added recitation was previously recited in a dependent claim.

The amendments were not made earlier because Applicants believed the amendments and comments filed in response to the Office Action dated January 5, 2004 were sufficient to overcome the enablement rejection, discussed below. The amendments are also believed to place the claims in condition for allowance or in better condition for appeal.

The Rejection of Claims 60-62, 70-75, and 81-87 Under 35 U.S.C. § 112, ¶ 1

Claims 60-62, 70-75, and 81-87 stand rejected under 35 U.S.C. § 112, first paragraph, as not enabled for their full scope. Claim 70 has been canceled. Applicants respectfully traverse the rejection as applied to claims 60-62, 71-75, and 81-87.

The rejected claims are directed to transgenic mice comprising a dominant negative allele of a *PMS2* mismatch repair gene which comprises a truncation mutation and methods of making and using such mice.

The Office Action asserts that claims 60-62, 71-75, and 81-87 are not enabled for their full scope. "The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims." Final Office Action at page 3, lines 2-5. To conclude that the claims are not enabled, the Patent Office must determine if one of skill in the art would be able to make and use the entire scope of the claimed invention without resorting to undue experimentation. *In re Wright*, 999 F.2d 1561 (Fed. Cir. 193). See also M.P.E.P. § 2164.08. The Federal Circuit has enunciated eight factors to be considered in determining if practice of an invention requires undue experimentation. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). These factors include:

- the quantity of experimentation necessary to make or the use the invention based on the content of the disclosure;
- the amount of direction provided by the inventor in the application;
- the presence of working examples of the invention in the application;
- the nature of the invention;
- the state of the prior art;
- the relative skill of one of those in the art;
- the predictability or unpredictability in the art; and
- the breadth of the claimed invention.

Id. An enablement analysis must consider all the evidence related to each of the factors, and a conclusion of nonenablement must be based on the evidence as a whole. *Id.*

Direction presented in the application and predictability in the art

The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839 (C.C.P.A. 1970). The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. M.P.E.P. § 2164.03. In fact, what is well known in the art need not be disclosed and is best omitted. *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991). See also M.P.E.P. § 2164.08.

The application provides sufficient guidance to one of skill in the art such that he or she would be able to make and use transgenic mice comprising a dominant negative *PMS2* allele comprising a truncation mutation. The specification discloses that methods of making transgenic animals were known at the time the application was filed and briefly describes methods of making such transgenic animals. The specification discloses:

> Any method for making transgenic animals known in the art can be used. According to one process of producing a transgenic animal,

> the polynucleotide is injected into a fertilized egg of the animal and the injected egg is placed into a pseudo-pregnant female. The egg develops into a mature animal in which the polynucleotide is incorporated and expressed. The fertilized egg is produced in vitro from the egg and the sperm of donor animals of the same species as the pseudo-pregnant female, who is prepared by hormone treatments to receive the fertilized egg and become pregnant. An alternative method for producing transgenic animals involves introducing the polynucleotide into embryonic cells by injection or transfection and reintroducing the embryonic cells into the developing embryo.

Page 9, lines 21-31. One of skill in the art would have been able to produce transgenic mice based on the disclosed methods provided in the specification.

Furthermore, as indicated in the specification, the art had developed methods of predictably producing transgenic mice prior to the effective filing date of the application, April 14, 1998. U.S. Patent No. 6,339,183 (filed November 1997), of record, teaches production of a transgenic mouse expressing a uroplakin II gene. See Example 2 at column 9, line 7 to column 10, line 5. U.S. Patent No. 5,965,788 (filed June 1992), of record, teaches production of transgenic mice expressing human growth hormone. See Example 3 at column 7, lines 10-35. U.S. Patent No. 5,912,411 (filed June 5, 1995), of record, teaches production of transgenic mice expressing the luciferase gene. See Example 6 at column 52, line 10 to column 54, line 2. In fact, laboratory manuals teaching how to produce a transgenic mouse had been published prior to the effective filing date of the application. One such manual is entitled "Manipulating the Mouse Embryo, A Laboratory Manual" Cold Spring Harbor Laboratory Press, 1986, ed. Hogan, Costantini, and Lacy. Thus there was a high degree of predictability in the art for methods of producing transgenic mice. Given the high level of predictability in the art of producing transgenic mice and the direction supplied in the application, one of skill in the art would have been able to make and use a transgenic mouse without recourse to undue experimentation.

One of skill in the art would also have been able to make and use a transgenic mouse in which the transgene is a dominant negative allele of a *PMS2* MMR gene comprising a truncation mutation. The disclosure in the application describes one such *PMS2* allele and further provides direction to one of skill in the art as to how to identify other such alleles. The specification discloses that *hPMS2-134* (a PMS2 gene encoding a truncation mutation at codon 134) exerts a dominant negative effect on MMR in cells: "An example of a dominant negative allele of a mismatch repair gene is the human gene *hPMS2-134*." Page 7, lines 2-4. The specification also provides direction to one of skill in the art as to how to identify further such *PMS2* alleles. The specification discloses, "Dominant negative alleles of a mismatch repair gene can also be created artificially, for example, by producing variants of the *hPMS2-134* allele or other mismatch repair genes." Page 7, lines 20-23. The specification also guides one of skill in the art as to how to test other potential dominant negative *PMS2* alleles comprising a truncation mutation. The specification discloses:

> Mutations [introduced due to a putative dominant negative *PMS2* allele] can be detected for analyzing for alterations in the genotype of the cells or animals, for example by examining the sequence of genomic DNA, cDNA, messenger RNA, or amino acids associated with the gene of interest. Mutations can also be detected by screening the phenotype of the gene. A mutant phenotype can be detected by identifying alterations in electrophoretic mobility, spectroscopic properties, or other physical or structural characteristics of a protein encoded by a mutant gene. One can also screen for altered function of the protein in situ, in isolated form, or in model systems.

Page 10, lines 15-23. Thus the specification directs one of skill in the art to a dominant negative *PMS2* allele comprising a truncation mutation, guides one of skill in the art to further potential dominant negative *PMS2* alleles comprising a truncation mutation, and guides one of skill in the art to assays that can be conducted to test whether a *PMS2* allele comprising a truncation

mutation is dominant negative. This disclosure provides sufficient direction to one of skill in the art to make and use a transgenic mouse comprising a dominant negative allele of a *PMS2* MMR gene, said *PMS2* MMR gene comprising a truncation mutation.

Further, the predictability of identifying a dominant negative allele of a *PMS2* MMR gene comprising a truncation mutation was sufficiently high at the time the application was filed to support applicants' contention that the specification provides adequate direction to enable the claims. As indicated above, a human *PMS2* allele having a truncation mutation and able to exert a dominant negative effect on MMR activity was disclosed, *i.e.*, human *PMS2-134*. Applicants have supplied the Patent Office with a declaration of Dr. Nicholas C. Nicolaides, of record, that teaches that an *Arabidopsis thaliana PMS2* allele comprising a truncation mutation at codon 134 (ArPMS134) induces a dominant-negative phenotype in bacteria. The fact that truncation mutants of *PMS2* homologues from widely disparate species such as human and *A. thaliana* plants induce hypermutability in cells provides evidence of strong conservation of the MMR pathway among species and that *PMS2* alleles truncated after the sequence coding for amino acid residue 134 will predictably exert a dominant negative effect on MMR activity in cells. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. M.P.E.P. § 2164.03. Furthermore, other dominant negative alleles of *PMS2* comprising a truncation mutation were known in the art before the effective filing date of the application. Pang (*Mol. Cell. Biol.* (1997) 17:4465-4473), of record, teaches that yeast *Pms1p*, a homolog of *PMS2*, truncated to encode amino acid residues 692-904, exerts a dominant negative effect on MMR activity. See Table 1 on page 4470. Thus, the high degree of predictability in the art and the direction provided by the applicants in the specification indicates that one of skill in the art would have been able to (1)

produce transgenic mice that (2) comprise a dominant negative allele of PMS2 comprising a truncation mutation without recourse to undue experimentation.

The Presence of Working Examples

While the present specification does not provide working examples of the claimed transgenic mice, compliance with the enablement requirement does not hinge on the presence or absence of working examples or a description of all embodiments of the invention. M.P.E.P. § 2164.02. Applicants are permitted to provide a declaration after the filing date which demonstrates that the claimed invention works so long as the steps, materials, and conditions used in the experiments of the declaration are commensurate in scope with the specification and that which was known to one of skill in the art. M.P.E.P. § 2164.05. In accordance with these principles, Applicants submitted the declaration of Dr. J. Bradford Kline to support the enablement of the claims. The declaration of Dr. J. Bradford Kline describes the production of transgenic mice comprising a dominant negative allele of human *PMS2* comprising a truncation mutation (*PMS2-134*) using methods described in the specification. Applicants further submitted a supplemental declaration of Dr. J. Bradford Kline, of record, describing the phenotype of these mice. The supplemental declaration describes the mice as having a hypermutable phenotype, consistent with the specification and claims.[1] Thus applicants have submitted evidence equivalent to a working example that weighs in favor of enablement of the claims.

[1] The final Office Action asserts that one of skill in the art would not have been able to use the claimed mouse because the "claimed invention encompasses any dominant negative allele of a PMS2 mismatch repair gene comprising any truncation mutation and applicants' specification does not provide any guidance as to what would be the phenotype of such mice." Page 3, lines 24-27. Applicants respectfully point out that the specification discloses the phenotype of the claimed mice at page 7, lines 28-31: "A cell or an animal into which a dominant negative allele of a mismatch repair gene has been introduced will become hypermutable. This means that the spontaneous mutation rate of such cells or animals is elevated compared to cells or animals without such alleles." Applicants further direct the Patent Office to the pending claims, each of which is directed to or otherwise recites a "hypermutable, transgenic mouse."

The relative skill of those in the art and the state of the prior art

As discussed above, at the time of the effective filing date of the application, methods of predictably producing transgenic mice and predictably producing dominant negative PMS2 alleles comprising a truncation mutation were known in the art. Because these were predictable, the relative skill in the art and the state of the art were also high at the time the application was filed. These factors weigh in favor of enablement of the claims.

Quantity of Experimentation

The test for determining whether a quantity of experimentation is unreasonable is not merely quantitative. A considerable amount of experimentation is permissible if it is merely routine or if the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

As indicated above, the specification describes several methods of making transgenic mice. These, and other, methods of producing transgenic mice were also known in the art at the time the application was filed. Thus, methods of making transgenic mice were somewhat routine. Making the claimed transgenic mice would have required no more experimentation than that routinely employed in the art.

Also indicated above, the specification describes a dominant negative allele of *PMS2* comprising a truncation mutation. Several other dominant negative alleles of *PMS2* that encoded truncated PMS2 were also known to those of skill in the art and the specification teaches how to identify further such *PMS2* alleles. The identification of further *PMS2* alleles would be performed by well-known, routine, methods as described in the specification. See specification at page 10, lines 15-23, quoted above. Therefore, even if, *arguendo*, considerable

experimentation would have been required to identify additional dominant negative alleles of *PMS2* comprising a truncation mutation or to produce a transgenic mouse comprising such a dominant negative allele, it would not have been undue. Rather, such experimentation would merely be routine to those of skill in the art. Thus, the amount of experimentation that would have been required to make and use the claimed invention weighs in favor of enablement

Examination of the evidence as a whole of the *Wands* factors weighs in favor of enablement of the claims.

Applicants respectfully request withdrawal of the rejection.

Respectfully submitted,
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